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DAYTIME SLEEP AIDS AND NIGHTTIME COGNITIVE PERFORMANCE

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Air and ground crews are often given rest opportunities at atypical times, outside of a normal entrained circadian sleep period. Due to normal human biology, this practice often leads to delayed, thus shortened, sleep as well as restless sleep. In such cases, a sleep promoting or "No-Go" medication may be prescribed to promote a more restorative crew rest. This study compared two doses of the hypnotic zolpidem, two doses of melatonin and placebo for their effects on daytime sleep, on nighttime cognitive performance and on mood in an operationally and militarily relevant paradigm. The participants worked all night. Subsequently, an Early Group slept from 0800-1600 and a Late Group slept from 1400-2200. The participants worked all night again. Measures included polysomnography, simple and complex cognitive task performance, vigilance, subjective reports, salivary melatonin, and vital signs. Neither zolpidem nor melatonin was successful in improving daytime sleep compared to placebo. Participants slept longer under the medicated treatments, but it was not statistically significant. Sleep inertia was deepened by the use of zolpidem and may prolong degraded performance, sleepiness and fatigue. In this study, there were no advantages for morning or afternoon sleepers for nighttime alertness, mood or performance. The Foret & Lantin (1972) findings of 3-4 hours of sleep during the day do not appear to hold for sleep-deprived people sleeping under ideal conditions. For two consecutive work nights, ideal daytime sleeping conditions appear to provide nearly as much sleep as a sleep aid and without any risk to nighttime performance or side effects.

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PREFACE

This report covers the project period of 1 May 2001 to 30 November 2005. The work was performed under Job Order Number 71845901. The work was performed by:

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SUMMARY

Air and ground crews are often given rest opportunities at atypical times, outside of a normally entrained circadian sleep period. Due to normal human biology, this practice often leads to delayed, thus shortened, sleep as well as restless sleep. In such cases, a sleep promoting or "No-Go" medication may be prescribed to promote a more restorative crew rest. The study reported here compared two doses of the hypnotic zolpidem, two doses of melatonin and placebo for their effects on daytime sleep, on nighttime cognitive performance and on mood in an operationally and militarily relevant paradigm. The participants worked all night. Subsequently, an Early Group slept from 0800-1600 and a Late Group slept from 1400-2200. The participants worked all night again, and recovery sleep was monitored the following day and night without sleep aids. Measures included polysomnography, simple and complex cognitive task performance, vigilance, subjective reports, salivary melatonin, and vital signs. Neither zolpidem nor melatonin was successful in improving daytime sleep compared to placebo. Participants slept longer under the medicated treatments, but it was not statistically significant. Given the sleep outcome, it was not surprising that there were no differences among the sleep aid conditions for alertness, mood or performance. Sleep inertia was deepened by the use of zolpidem and may prolong degraded performance, sleepiness, and fatigue. In this study, there were no advantages for morning or afternoon sleepers for nighttime alertness, mood or performance. The Foret & Lantin (1972) findings of 3-4 hours of sleep during the day do not appear to hold for sleep-deprived people sleeping under ideal conditions. For two consecutive work nights, ideal daytime sleeping conditions appear to provide nearly as much sleep as a sleep aid and without any risk to nighttime performance or side effects.

Key words: zolpidem, melatonin, day sleep, night work, polysomnography, cognitive performance, synthetic work, vigilance, PVT, melatonin

Daytime Sleep Aids and Nighttime Cognitive Performance

INTRODUCTION

Air and ground crews are often given rest opportunities at atypical times, outside of a normally entrained circadian sleep period. Due to normal human biology, this practice often leads to delayed, thus shortened, sleep as well as restless sleep. The physical and psychological restoration associated with these unusual sleep times is often insufficient for normal performance efficiency. For normally entrained individuals accustomed to sleeping at night, sleep in the late morning is difficult while sleep in the afternoon is somewhat easier (Foret & Lantin, 1972). In such cases, a sleep promoting or "No-Go" medication may be prescribed to promote a more restorative crew rest. One compound recently approved in 1997 to promote sleep during adverse operational situations in military aviators was zolpidem. Another compound, the hormone melatonin, was not approved for use in aircrew but has found wide acceptance as a sleep-inducing compound in the general public (Hughes, Badia, French, Santiago, & Plenzler, 1994). It is possible that either zolpidem or melatonin could be used to facilitate rest for crews at risk for mission-induced insomnia. Although zolpidem has been fielded by the Air Force, its efficacy as a fatigue countermeasure has not been systematically tested in simulated military work-rest scenarios nor has it been compared with melatonin.

From the literature (Foret & Lantin, 1972; Pollard, 1996; Reid, Roach & Dawson, 1997) it was reasoned that attempting to sleep during the morning or afternoon would result in three to four hours of sleep at best. From AF operations we learned that fighter pilots trained at night, two to three nights in a row (Red Flag), with sleep during the day complained of fatigue each night. It was, therefore, hypothesized that sleep aids given during daytime sleep would lengthen and improve sleep and lead to improved performance at night.

Zolpidem

Zolpidem tartrate (Ambien®) is an imidazopyridine manufactured in 5 and 10 mg doses (Searle Pharmaceutical Company). It differs structurally from the classic benzodiazepines and yet has sedative and anxiolytic effects that may be mediated through selective benzodiazepine BZ(1) Omega(1) receptors (Griebel, Perrault, Letang, Granger, Avenet, Schoemaker, & Sanger, 1999). It is a strong sedative with only minor anxiolytic, myorelaxant and anticonvulsant properties, and has been shown to be effective in inducing and maintaining sleep in adults with various sleep pathologies (Salva & Costa, 1995). These studies further suggest that zolpidem produces no rebound or withdrawal effects and study participants have experienced good daytime alertness after 20-mg oral doses given at night. Peak plasma concentrations were reached 45 minutes after ingestion (Salva & Costa, 1995). The elimination half-life averages about 2.6 hours (Sanofi-Synthelabo, 2002). Zolpidem has no known contraindications. Additive effects on psychomotor performance occur with other known CNS depressants such as alcohol (Sanofi-Synthelabo, 2002).

This profile makes zolpidem a good alternative to the comparatively long lasting benzodiazepine temazepam (Restoril®), currently the only other choice for operationally induced insomnia in USAF aircrew (AFMOA/CC Memorandum, 2001). However, the sedation induced by zolpidem

and temazepam is the result of central nervous system (CNS) depression, and crews may be ineffective until the compound wears off, which is dependant on time since ingestion. Military personnel experiencing an unexpected emergency or attack may be severely impaired in their ability to perform their normal tasks.

The operational environment where zolpidem may be used ranges from a quiet room at a hotel to a bunk on a jet aircraft during flight. The noise and light that may be encountered under some of these conditions may prevent sleep even with 10 mg of zolpidem. Therefore this experiment used 10 and 20 mg doses and examined the dose-response relationship.

The incidence of zolpidem side effects expressed as a percentage of those surveyed in 11, short-term, placebo-controlled, clinical trials is shown in Table 1.

Table 1. Percentage of respondents indicating zolpidem side effects.

Adverse Event	Zolpidem (N = 685)	Placebo (N = 473)
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Nausea	2	3
Diarrhea	1	-
Myalgia	1	2
Source: Sanofi-Synthelabo Inc. website (2002).		

Zolpidem is metabolized primarily by the cytochrome P450 (CYP) 3A4 enzyme in the liver and to a clinically insignificant extent by the CYP1A2 and CYP2D6 enzymes. Known drug interactions occur with fluoxetine (Prozac®), itraconazole (Sporanox®), rifampin (Rifadin®), and sertraline (Zoloft®). Grapefruit juice and green tea can partially inhibit zolpidem metabolism. Liver disease can decrease the metabolism of zolpidem but this condition is not compatible with aircrew selection criteria (Sanofi-Synthelabo Inc., 2002).

Zolpidem is classed as Category B for use during pregnancy: this drug should be used during pregnancy only if clearly needed. No human reproduction studies have been done with zolpidem. Untoward maternal and fetal effects were noted in rats and rabbits, but only with repeated dosing at doses greater than 100 times those proposed here. The no-effect dose for fetal toxicity in rats and rabbits was 5 and 7 times the maximum human dose respectively on an mg/kg basis.

Melatonin

The naturally occurring hormone melatonin has received widespread public support as a safe and non-prescriptive means to induce sleepiness with typical doses of 3-10 mg. It has the distinct military advantage of not promoting sleep by CNS depression that would preclude personnel from going on duty before drug washout. Melatonin is primarily synthesized and secreted by the pineal gland but also produced in other tissues such as the retina (Morgan, Barrett, Howell & Helliwell, 1994). High affinity melatonin receptors (Mel 1a) have been found in vertebrate brain and retina. Its signal transduction effects may be mediated through G-protein coupled

mechanisms that reduce intracellular cyclic AMP (Morgan, et al., 1994). Melatonin may also play a role in altering calcium levels in cells throughout the body. The mean peak plasma level for melatonin occurs about an hour after ingestion and the elimination half-life is about 2-3 hours across a wide variety of doses (Dawson, Gibbon & Singh, 1996). This gives melatonin a pharmacokinetic profile comparable to zolpidem.

It is likely that melatonin plays a role in regulating sleep-wake cycles (Shochat, Luboshitzky & Lavie, 1997). In one study, a dose of 10 mg was as effective as a 40-mg dose in promoting sleep (Hughes, Badia, French, Santiago & Plenzler, 1994). Conversely, bright light can inhibit the pineal production of melatonin and subsequently cause a delay in the circadian rhythm. In cultured hamster retinal cells, serotonin receptor agonists were shown to block the effect of bright light (Rea & Pickard, 2000) and dopamine and dopamine agonists to inhibit the release and/or synthesis of melatonin (Tosini & Dirden, 2000). Two concerns exist about using melatonin under operational conditions:

1. Melatonin may not be as effective as a true sedative in inducing sleep, particularly when phase advancing the circadian rhythm.
2. The impact on cognitive performance needs to be gauged in the context of a military scenario and on tasks that have operational realism.

Melatonin is widely available over the counter as a nutritional supplement and is classified by the Food and Drug Administration (FDA) as an "other dietary substance." It is "generally recognized as safe" by the FDA. Melatonin was also classified as an "orphan" drug for the treatment of circadian rhythm-related sleep disorders in blind patients (Drug Digest website, 2004).

Melatonin has no known contraindications. It has been administered in doses as high as 250 mg/day with no evidence of toxic effect on the eyes, liver, kidneys, or bone marrow. The only reported side effect was drowsiness. Melatonin given at the highest doses for 25-30 days showed some depression of serum luteinizing hormone levels and may decrease growth hormone release in response to stress. The no-effect dose for maternal toxicity in rats was 100 mg/kg/day and for fetal toxicity was 200 mg/kg/day. These were the lowest doses producing an effect and were noted to occur during gestational days 12-18 (Drug Digest website, 2004).

Known drug interactions with melatonin include decreased synthesis after administration of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen. Propranol and diazepam also inhibit melatonin synthesis. Melatonin release is stimulated by the monoamine oxidase-A (MAO-A) inhibitors clorgyline and trancypromine, but not the MAO-B inhibitor selegiline. Melatonin synthesis/release is increased by α-2 adrenoreceptor agonists, the combination of tryptophan plus serotonin releasing drugs with or without MAO inhibitors, and aminophylline. Melatonin can elevate blood pressure in patients previously well controlled with sustained release nifedipine (Drug Digest website, 2004). Of these medications only NSAIDs were permitted for use by aircrew without a medical waiver. Therefore any current or within the past 60 days use of these medications was disqualifying for participation as a participant. Participants were advised not to use NSAIDs during the study. Participants were given a sheet

listing all do's and don't during the conduct of the study and they were quizzed on these prior to each data collection session.

Hypotheses

The study was designed to provide cognitive performance and other data on the impact of two sleep-promoting compounds at two doses in the context of a military scenario. An additional purpose was to use this data to develop an algorithm for the Fatigue Avoidance Scheduling Tool (FAST) to predict sleep aid effects on performance effectiveness. Through the Small Business Innovative Research (SBIR) program, the Air Force has sponsored the development of FAST that predicts cognitive performance effects related to sleep quantity, quality, timing, and circadian rhythm. Because of interest in fatigue countermeasures, the AF would like to include the sleep aid effects on performance in the tool's model.

All study participants were deprived of sleep for one night and then allowed to sleep during the next day. All participants in each group received all five-drug treatments during five separate weeks of testing. An Early Sleep Group (AM) slept from 0800-1600; a Late Sleep Group (PM) slept from 1400-2200.

Specific hypotheses were that:

- Zolpidem and melatonin treatments (both doses of each) will generate more total slow-wave sleep (SWS) than the placebo treatment.
- A zolpidem treatment will generate more total SWS and sleep time will be longer than a melatonin treatment.
- Zolpidem and melatonin treatments will perform better overall than a placebo treatment during simulated night operations (testing).
- The early sleep group will generate less total SWS than the late (afternoon) sleep group.
- The early sleep group will perform more poorly during the simulated night operations (testing) than the late sleep group.

METHODS

Participants

Volunteer participants were recruited by posting notices at local universities, colleges, and military bases, and by contacting individuals who had volunteered previously for similar studies. Veridian Engineering provided temporary employment for the participants. Under Contract F41624-97-D-6004 with the AF, they had insurance coverage that was specified by FAR 28.307-2, Liability, and contemplated by FAR 52.228-5, Insurance—Work on a Government Installation, and 52.228-7, Insurance—Liability to Third Persons. The FARs and insurance documents were available for the participants to view at the time of recruiting and during the study.

The participants consisted of 16 healthy individuals, participating in four groups of four, and recruited from the San Antonio area. Males and females between the ages of 18 and 40 years were recruited. All participants were screened for age and past medical history. Each participant was paid $10 per hour for the 9 hours of training, the 9 hours of baseline sleep and the 302.5 hours of study testing (5 sessions lasting 60.5 hours each), for the hours they completed. Their maximum possible total compensation was $3,205.00 ($10 x 320.5 hours). All candidate participants were screened medically to avoid complications from drug interactions with zolpidem or melatonin that might cause harm to the participant or possible experimental confounding. Volunteers could not have a history of liver disease and current or recent use of medications. Only medications allowed for use by aircrew per AFI 48-123 were permitted. Of the allowed and waiverable medications only erythromycin and intranasal or topical glucocorticoids posed any potential for interaction with zolpidem. Therefore, any current or within the past 60 days use of these medications were disqualifying for participation. Participants were advised not to consume grapefruit juice or green tea during the study. Participants who acknowledged significant sleeping difficulties were excluded, as well as participants who admitted to the use of any sleep medication, or medications used in the treatment of narcolepsy or depression. Information about the study was mailed to each qualified volunteer. Female participants who chose to participate in this study were required to submit to a urine pregnancy test within 36 hours prior to each experimental session. The result had to be negative to participate.

Facility

The investigation was carried out in the AFRL/HEPF Fatigue Countermeasures Lab (FCL) at Bldg. 1192, Brooks City-Base. The FCL was developed to provide a temporal isolation facility for conducting research and development activities on fatigue countermeasures that extend and enhance warfighter cognitive performance and physical endurance during sustained aerospace operations. Some of its characteristics and capabilities include: 2,000-sq-ft lab with four bedroom-bathroom areas, participant monitoring through sophisticated audio/video systems, cognitive performance assessment instruments for individual and/or group performance, physiological measurement capabilities including EEG, polysomnography, body temperature, blood pressure, HR, vestibular function, strength, and endocrine levels.

Tests and Dependent Measures

Cognitive Tasks
Unmodified PC computers, Pentium 3 class, were used to administer the Automated Neuropsychological Assessment Metric (ANAM) battery of cognitive tests. The 18-minute battery used the following tests:

Simple Reaction Time. This test presents a simple stimulus on the screen (*) and the participant is instructed to press the left mouse button each time the stimulus is presented. The duration of the task was approximately 20 seconds.

Continuous Performance Test. This test is a continuous letter comparison task (Stanny, 1990) in which the subjects are asked to monitor a randomized sequence of digits, 0 through 9. The letters are presented one at a time in the center of the screen. Subjects are asked to continuously monitor the numbers and press the left mouse button if the letter on the screen matches the letter that immediately preceded it. They are requested to press the right mouse button if the number doesn't match the immediately preceding letter. The duration of the task was approximately three minutes.

Mathematical Processing. During this task, arithmetic problems are presented in the middle of the screen. The task involves computing an answer, making a decision, and responding. Each problem includes two mathematical operations (addition and/or subtraction) on sets of three, single-digit numbers (e.g., 5 + 3 - 4 = ?). The subject is instructed to read and calculate from left to right and indicate whether the answer is greater-than or less-than five by pressing the left or right mouse buttons. The operators and operandi are selected at random with the following restrictions: only the digits 1 through 9 are used; the correct answer may be any number from 1 to 9 except 5; greater-than and less-than stimuli are equally probable; cumulative intermediate totals have a positive value; working left to right the same digit cannot appear twice in the same problem unless it is preceded by the same operator on each occasion (e.g., +3 and +3 are acceptable, while +3 and -3 are not); the sum of the absolute value of the digits in a problem must be greater than 5. Task duration was three minutes.

Logical Reasoning – Symbolic. This test is an adaptation of the task developed by Baddeley (1968). It is a linguistic task requiring knowledge of English grammar and syntax. It also requires the ability to determine whether various simple sentences correctly describe the relational order of two symbols. This implementation differs from the original paper and pencil version in that stimulus pairs are presented one at a time and are screen-centered rather than left-justified to reduce differences in visual search times. On each trial the symbol pair "# &" or "& #" is displayed along with a statement that correctly or incorrectly describes the order of the letters as depicted in the example below:

&#

is first

The subject decides as quickly as possible whether the statement is true or false and then presses the left mouse button for true or the right mouse button for false. Task duration was three minutes.

Matching To Sample. Matching to Sample is a test in which the subject is required to match a block pattern from memory. A single 4 x 4 matrix (i.e., a checkerboard) is presented in the center of the screen as a sample stimulus. For each presentation, the matrix contains eight cells colored red and eight colored aqua, in quasi-random pattern. Following 5.0 to 5.1 seconds, two comparison matrices are presented side by side. One of the comparison matrices will match the "sample" matrix, while the other comparison matrix will differ in shading from the "sample" by one cell. The subject's task is to indicate, by pressing the left or right mouse button, the matrix that matches the "sample" matrix. The sample matrix duration was set to 3000 ms and timeout occurred at 3100 ms for the comparison matrices. Task duration was three minutes.

Other Tests

Psychomotor Vigilance Test (PVT). Vigilance performance was assessed using the Psychomotor Vigilance Task (PVT; Dinges, 1992; Vigilance Task Monitor, Model PVT-192, CWE, Inc., Ardmore PA, available from Ambulatory Monitoring, Inc., Ardsley NY). The PVT required sustained attention and discrete motor responses. It is a brief, high signal load, reaction time task that is sensitive to many minor cognitive stresses, including fatigue due to sleep loss, circadian variation, and shift work. The 8" x 4.5" x 2.4" portable, battery-operated device ran a continuous simple reaction time test for ten minutes. The participant's job was to watch a digital counter on the device and, when the counter started to run, to turn off the counter as quickly as possible by pressing a button. The task was presented in the visual-only (0.5-inch LED) mode. The pseudo-random interstimulus interval was 2 to 12 seconds and the test lasted 10 minutes. The variables provided by the PVT-192 included the number of stimuli presented, the mean of the reciprocals of all reaction times, mean reaction time, the mean of the reciprocal of the slowest 10% of reaction times, the standard deviation of the RT, the number of false alarms, and the number of lapses (reaction times slower than 500 msec) (Dinges, Pack, Williams, Gillen, Powell, Ott, Aptowicz, & Pack, 1997).

Complex Task. The fatigue sensitivity of a complex cognitive task, SynWork, was determined over 18 minutes of testing. SynWork contains simultaneous tasks that require many of the skills exercised by a pilot flying various aircraft missions. The ANAM SynWork test presents four neurocognitive tasks simultaneously. This program was designed to provide an intermediate assessment system that bridges the gap between basic-construct test batteries and million-dollar operation-specific simulators. The tasks comprising the initial Synwork program were selected to provide a generic work environment where the operator was required to remember and classify items on demand (the Sternberg Memory Scanning Task), solve self-paced arithmetic problems, and continuously attend to both a visual and auditory monitoring task. SynWork is intended to provide a generic PC-based synthetic work task. Synwork was not designed to simulate a specific job or system. However, it does hold potential for providing a means for developing a fitness to stand duty criterion for watch-standing jobs in particular. SynWork provides a way to assess divided attention and resource allocation.

Subjective Data.
Mood and subjective ratings data were acquired from each participant throughout the experimental sessions.

Stanford Sleepiness Scale (SSS). According to Mitler, Carskadon MA, & Hirshkowitz (2000), the "Advantages of the SSS include its brevity and ease of administration and the fact that it can be administered repeatedly. To use the SSS (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973), the participant selects one of seven sets of Likert-scale descriptors, ranging from 1, "Feeling active and vital; alert; wide awake," to 7, "Almost in reverie; sleep onset soon; lost struggle to remain awake." The version used in ANAM was derived from the Walter Reed Performance Assessment Battery (WRPAB, Thorne, Genser, Sing & Hegge, 1985). The descriptive statements have been simplified and altered to make them education and culture neutral. A rating of 5 or above is often causing for concern with respect to acceptable job performance. A SSS rating is acquired from the participants every few hours while they are awake. We acquired the SSS score for analyses of sleep quality and circadian variation. The ANAM 2001 version of the Sleepiness Scale is presented below.

"Choose the statement below that best describes how you feel right now."

1. Feeling very alert, wide awake, and energetic.
2. Able to concentrate, but not quite at peak.
3. Relaxed, awake, responsive, but not fully alert.
4. A little foggy and mild difficulty concentrating.
5. Foggy, slowed down, beginning to lose interest in remaining awake.
6. Sleepy, woozy, prefer to be lying down; fighting sleep.
7. Sleep onset soon, losing struggle to remain awake.

Mood Scale 2-R. This test was derived from a paper-and-pencil adjective checklist constructed and validated by Ryman, Biersner, and LaRocco (1973). The computerized version was derived from the WRPAB (Thorne, Genser, Sing & Hegge, 1985). The ANAM Mood Scale2-R (MS2-R) includes adjective replacements that balance items in the six subscales. The current ANAM version of MS2-R consists of a listing of 36 adjectives. Participants are asked to respond by pressing 1, 2, or 3 on the computer keyboard, (i.e., "press 1 for yes, 2 for somewhat, and 3 for no") in response to the question, "How does the word shown below describe how you feel right now." Scores for six scales are produced and include Activity, Happiness, Depression, Anger, Fatigue, and Fear (i.e., anxiety). The Mood 2-R adjectives are shown in Table 2.

Table 2. Mood 2-R Adjectives.

Activity	Happiness	Depression	Anger	Fatigue	Fear (anxiety)
Energetic	Good	Miserable	Grouchy	Inactive	Uneasy
Lively	Content	Discouraged	Enraged	Weary	Alarmed
Alert	Cheerful	Depressed	Annoyed	Drowsy	Insecure
Spirited	Satisfied	Sad	Angry	Tired	Afraid

Active	Pleased	Downcast	Furious	Sluggish	Nervous
Steady	Happy	Gloomy	Irritated	Lazy	Anxious

Warfighter Fatigue Countermeasures (WFC) Drug Symptom Checklist. The WFC Drug Symptoms Checklist was created by using a standard drug symptom list but adding other questions of the participant related to the study. It contained 56 items with seven rating levels for each item. It also asked if the drug was perceived to be the source of symptoms and if the symptoms would interfere with job performance. The checklist was used to acquire data about the perceived effects of zolpidem and melatonin.

Physiological Data.

Polysomnograophy. Sleep onset and quality during sleep periods were assessed with ambulatory electrophysiological equipment. Electroencephalogical (EEG) signals were acquired from the C3-A2 and the O1-A1 scalp leads of the International 10-20 system using a Stellate Notta ambulatory recorder system (Stellate Systems, Inc., Montreal Quebec, Canada). In total, 14 skin surface electrodes were applied (6 scalp, 2 mastoid, 2 outer canthi, 2 chin, 2 ground). The EEG, electromyogram and electrooculogram signals were digitized at 128 samples/sec and sleep staging was coded by a registered polysomnographic technologist. Sleep latency, total sleep time, and sleep efficiency were assessed using the Stellate Harmonie software (Stellate Systems, Inc.)

Actigraphy. An Actigraph (Ambulatory Monitoring, Inc., Ardsley NY) was worn on the wrist. A small accelerometer within systematically recorded the individual's movement over time, both while awake and asleep. Actigraph data provide an effective means to identify sleep behavior patterns (Cole, Kripke, Gruen, Mulaney, and Gillin, 1992). Participants wore actigraphs for three days prior to and three days after each treatment period to assure that the participants did not have atypical sleep activity patterns.

Hormones. Salivary samples were collected using 10-cc test tubes. Participants were asked to aspirate a 3 ml saliva sample into the tube every two hours awake during the test phase. These samples were then refrigerated for later analysis for melatonin content. Appendix A describes the analysis process done by the Yerkes Research Center, Endocrine Core Lab at Emory University, Atlanta, GA. The Saliva Melatonin RIA kits came from ALPCO Diagnostics, Windham, NH.

Activity Log. The activity log (Appendix B) was used to provide sleep histories and subjective fatigue ratings for each participant. Participants were asked to indicate their fatigue state every two hours and to indicate when they slept. The log was completed for three days prior to and three days after each experimental session to assure the participants did not have atypical sleep activity patterns.

Vital Signs. Blood pressure, temperature, and heart rate were recorded often to examine physiological status when awake. Any measurement exceeding the values set forth in AFRL/HEP Operating Instruction 44-119, "Medical Education and Research: Human Subjects in Research" required notification of the medical monitor. A standard automated blood pressure

cuff and oral electronic thermometer were used (IVAC Vital-Check, Model #4415, by ALARIS Medical Systems). Oral temperature samples were closely coordinated with the saliva sample.

Experimental Design

The experiment was structured as a mixed, 2-factor, 2 x 5-level factorial with repeated measures on the second factor (Factor B). Factor A was Sleep Schedule (early vs. late) and Factor B was Dose (placebo, melatonin 5 and 10 mg and zolpidem 10 and 20 mg). Incorporated within the Dose factor was the expected ability to partition variance for comparing placebo, sedation by CNS depression with zolpidem, and natural sedation with melatonin. Because of the differences in time of testing, data from the two sleep times could not be unambiguously compared.

The experiment was designed to be sensitive to a one-standard-deviation effect size for a two-tailed test at a confidence level of (alpha = 0.05), 1 - alpha = 95% and a power of 1 - beta = 78% (Cohen, 1988, Table 2.3.2, Formula 12.2.1). This design required a sample size of 16. If r = 0.50 for repeated measures within Factor B, the power of those tests should be approximately 97% (ibid, Formula 2.3.9).

Procedures

The experimental work-rest schedule emulated a night-flying procedure used in the first quarter of FY01 at Red Flag (Lt Col Gibbons, personal communication) that, in turn, emulated intra-theater combat procedures used by Combat Air Forces. The Red Flag night-flying crews reported at 2300 to prepare for a 1.5-hour sortie within the 0300-0500 period, followed by a 2-hour debrief. In our procedures, the participants emulated flying a night sortie, followed by day sleep, a second night sortie followed by day work, and a recovery sleep night.

We assessed zolpidem at 10 and 20-mg oral doses and melatonin at 5 and 10-mg oral doses compared to placebo. During each of 5 weekly sessions, participants were given a single dose at either 0730 or 1330 hours before day sleep.

Participants were instructed to avoid drinking alcoholic beverages during the prior evening or afternoon of the scheduled sessions. Caffeinated drinks were not allowed during any test sessions. Decaffeinated soft drinks, water, and juice were offered for consumption. Participants were instructed to go to sleep between 2130 and 2200 hours the night before the scheduled test session, and to awaken between 0600 and 0700 hours. These instructions were intended to reduce variation in the amount of sleep participants obtain prior to the test session.

Participants were monitored closely to ensure their wakefulness throughout the test sessions. Participants were not allowed to sleep, doze, or "rest" their eyes at any time during their active participation in the study. They were asked to attempt their best performance at all times during testing sessions. Participants were asked to wear their actigraph device at all times during the six weeks of testing except when the devices were being serviced.

Participant Training. Participants were trained on all cognitive tests and the SynWork during training evenings prior to the first experimental session. They also had all equipment used

throughout the study demonstrated to them during the training sessions and were familiarized with the laboratory procedures including fire safety, power loss, illness, etc.

Participant Testing Schedule. Table 3 shows the schedule the participants followed in completing the research protocol. The schedule indicates times of data collection, sleep, eating and other breaks. Dose administration is indicated on a black background while sleep is indicated with a gray background. The full schedule represents the morning (AM) sleep group with the afternoon (PM) sleep group represented to the right showing all the events that took place on Saturday.

Table 3. Participant Experimental Session Schedule.

TIME	Wed	Thurs	Fri	Sat	Sun	Mon	Tues	Wed	Sat
0000				ANAM/	ANAM/				ANAM/
0100			S	PVT	PVT	S			PVT
0200			L	WinSyn	WinSyn	L			WinSyn
0300			E	ANAM/	ANAM/	E			ANAM/
0400			E	PVT	PVT	E			PVT
0500			P	Break	WinSyn	P			Breakfast
0600			WAKEUP	ANAM/PVT	ANAM/	ANAM/			ANAM/
0700				Dose (730)	PVT	PVT			PVT
0800	Normal	Normal	Normal	Bed Time	WinSyn	Discharge			WinSyn
0900					ANAM/				ANAM/
1000	Workday	Workday	Workday	S	PVT				PVT
1100				L	Lunch	Normal	Normal	Normal	Lunch
1200	Activities	Activities	Activities	E	ANAM/				ANAM/PVT
1300				E	PVT	Workday	Workday	Workday	Dose (1330)
1400	Monitor	Monitor	Monitor	P	Break				Bed Time
1500			with		WinSyn	Activities	Activities	Activities	
1600	with	with	Actigraphy	ANAM/	Break				S
1700				PVT	Dinner	Monitor	Monitor	Monitor	L
1800	Actigraphy	Actigraphy	Dinner	Dinner	Bed Time				E
1900			Testing	WinSyn		with	with	with	E
2000			ANAM/	ANAM/	S				P
2100			PVT	PVT	L	Actigraphy	Actigraphy	Actigraphy	
2200		Bed Time	ANAM/	WinSyn	E				ANAM/PVT
2300			PVT	ANAM/	E				Dinner
2400			WinSyn	PVT	P				WinSyn

Appendix C shows the timeline for a 6-week sequence for a flight of participants.

Dosing. All doses were oral and were given in a double blind procedure. The Ancillary and Clinical Pharmacy Flight of the Air Force Wilford Hall Medical Center prepared the medications and supported our double-blinding procedures. On the test day of each week, Day 2, zolpidem, melatonin or placebo were administered 30 minutes before retiring for their morning (AM) or afternoon (PM) 8-hr sleep. At the end of the experimental session on Monday, participants had a full week between test sessions for drug washout and recovery from fatigue.

There were (5! =) 120 possible orders of presentation for the five conditions (placebo, zolpidem 10 mg, zolpidem 20 mg, melatonin 5 mg, and melatonin 10 mg) and only 16 participants. To select from among these order possibilities, we used two randomization functions (RAND, RANDBETWEEN) available in Microsoft Excel®, with manual intervention to provide selection without replacement within each participant. The resulting presentation assignments are shown in Table 4.

Table 4. Scheme for 16 Psuedo-Randomized Orders of Presentation of Conditions to Participants.

Participant Number	Placebo	Melatonin 5 mg	Melatonin 10 mg	Zolpidem 10 mg	Zolpidem 20 mg
1	2	3	4	1	5
2	3	4	1	2	5
3	1	4	5	3	2
4	3	5	2	4	1
5	3	2	5	1	4
6	2	5	3	4	1
7	4	1	5	2	3
8	5	1	2	3	4
9	1	3	4	5	2
10	4	2	1	5	3
11	4	3	5	2	1
12	5	4	3	1	2
13	2	1	3	4	5
14	1	5	2	3	4
15	1	2	4	5	3
16	5	2	1	4	3
Total	46	47	50	49	48

RESULTS

In this experiment, we kept participants awake for one night with sleep during the following day at either 0800-1600 (morning) or 1400-2200 (afternoon). Testing was conducted the following night from 2200 to 0900 throughout the following day. Since the afternoon sleep group was awakened and tested at 2200, their 2200 data would be expected to suffer from the effects of sleep inertia. Therefore to make the two groups more comparable, only the data from 0000, 0300, and 0600 of the second night were used to compare the five drug treatment conditions for night work. Data collected immediately after awakening are examined in a later section of the report.

Fourteen participants between the ages of 21 and 44 (mean=28.6) completed the study. They were recruited from San Antonio, TX, primarily the military installations and universities. Table 5 shows a breakdown of the participants by their time of sleep.

Table 5. Distribution of Participants by Sleep Time

	Sleep Time		
Participants	**AM**	**PM**	**Totals**
Male	3	4	7
Female	3	4	7
Totals	6	8	14

Night Work Effects

Cognitive Performance and Vigilance

Five cognitive tests were used in this study: Simple Reaction Time, Logical Reasoning, Mathematical Processing, Continuous Performance and Delayed Match-to-Sample. The Mixed ANOVA for each dependent measure for each test included variables for Drug Treatment (5), Time (3) and Sleep Group (2). For each test, accuracy, reaction time (RT), standard deviation of RT (SDRT), throughput and percent of missed trials were analyzed. Results of the 23 ANOVA tests are shown in Tables 6-7. What is very clear is that none of the sleep aids given for daytime sleep improved nighttime performance compared with placebo. Figure 1 shows a graph of throughput for the Logical Reasoning Test. Throughput combines speed and accuracy into a single measure (Thorn, 1991). Even though throughput under the 20 mg zolpidem treatment appears to be more degraded at 0000 and 0300, there was no significant Drug or Drug by Time interaction, only a significant Time effect. This outcome was similar for Simple Reaction Time, Match-to-Sample and the Time effect for Mathematical Processing. Further, none of the measures showed an effect of Sleep Group. Cognitive performance levels were no different for sleep in the morning (0800-1600) or sleep in the afternoon (1400-2200). Further there were no significant interactions of Sleep Group with Time or Drug and there was no significant three-way interaction.

Table 6. Summary of Analysis for Simple Reaction Time, Logical Reasoning and Mathematical Processing

Dependent Measure – <u>Simple Reaction Time</u>	Drug F(4,44) = p =	Time F(2,22) = p =	Sleep Group F(1,11) = p =	Interactions F(df1,df2) = p =
Reaction Time	1.59 0.202	9.50 0.005*	0.284 0.605	None significant
SD of Reaction Time	2.69 0.069	10.98 0.001*	0.81 0.389	None significant
Percent of Missed Trials	0.96, 0.427	3.25, 0.063	3.97, 0.072	None significant
<u>Logical Reasoning</u>				
Accuracy	2.17 0.146	8.20 0.003*	0.33 0.578	None significant
Reaction Time	1.29 0.290	0.49 0.567	0.39 0.547	None significant
SD of Reaction Time	1.51 0.221	9.13 0.001*	0.187 0.673	None significant
Throughput	2.23 0.081	6.25 0.007*	0.22 .647	None significant
Percent of Missed Trials	1.13 0.331	4.22 0.028*	0.44 0.520	None significant
Note: * $p < 0.05$				

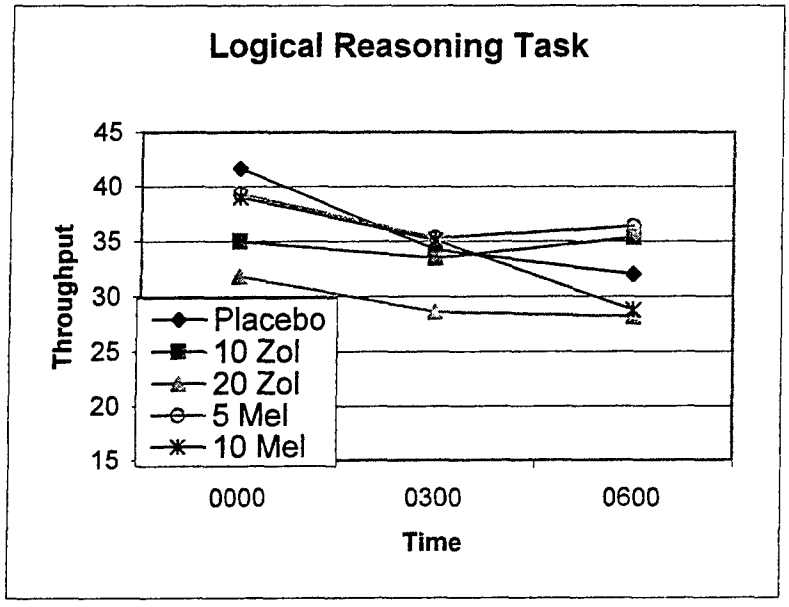

Figure 1. This graph of throughput from the Logical Reasoning Task is typical of the results of the cognitive tests showing the significant Time effect, but no drug or interaction effects. Performance degraded across the early morning hours regardless of the drug treatment given for the previous day's sleep.

Table 7. Summary of Analysis for Continuous Performance, Delayed Matching-to-Sample and SynWork.

Dependent Measure – Continuous Performance	Drug F(4,44) = p =	Time F(2,22) = p =	Sleep Group F(1,11) = p =	Significant Interactions
Accuracy	1.31 0.289	10.54 0.001*	0.12 0.741	None significant
Reaction Time	3.04 0.028*	2.66 0.092	1.00 0.338	None significant
SD of Reaction Time	3.08 0.025*	4.23 0.028*	1.75 0.213	None significant
Throughput	3.25 0.020*	13.58 0.001*	0.69 0.424	Drug x Time F(8,88) = 2.11 p = 0.043*
Percent of Missed Trials	1.77 0.170	9.02 0.001*	0.26 0.621	None significant
Mathematical Processing				
Accuracy	2.20 0.107	9.26 0.004*	0.07 0.803	None significant
Reaction Time	0.41 0.788	0.80 0.446	1.74 0.211	None significant
SD of Reaction Time	1.27 0.296	8.28 0.002*	0.55 0.475	None significant
Throughput	0.319 0.805	1.09 0.339	0.76 0.400	Time x Sleep Group F(2,24) = 4.07 0.045*
Percent of Missed Trials	2.73 0.070	5.97 0.011*	0.01 0.925	None significant
Delayed Match-to-Sample				
Accuracy	0.85 0.491	9.63 0.001*	0.54 0.480	None significant
Reaction Time	1.36 0.264	2.56 0.100	1.16 0.305	None significant
SD of Reaction Time	2.49 0.057	3.15 0.063	0.35 0.568	None significant
Throughput	0.76 0.538	10.34 0.001*	0.11 0.744	None significant
Percent of Missed Trials	1.13 0.320	1.96 0.167	0.07 0.799	None significant
SynWork Task				
Total Score	3.30 0.035*	9.23 0.001*	0.0 0.990	None significant
Note: * $p < 0.05$				

The only performance test showing a statistically significant Drug by Time interaction was Continuous Performance for the throughput measure shown in Table 7. Figure 2 shows that throughput was reduced for the zolpidem treatments and the 10 mg dose of melatonin at midnight (0000) compared with placebo. The 20 mg dose of zolpidem was also statistically lower than the 5 mg dose of melatonin at 0000. At 0300, only the two zolpidem treatments performed poorer that the placebo treatment. Again the high dose of zolpidem was degraded compared to the low dose of melatonin. Averaging across the Time factor, the means for throughput were 88 (Placebo), 87 (5 Mel), 79 (10 Mel), 77 (10 Zol), and 75 (20 Zol).

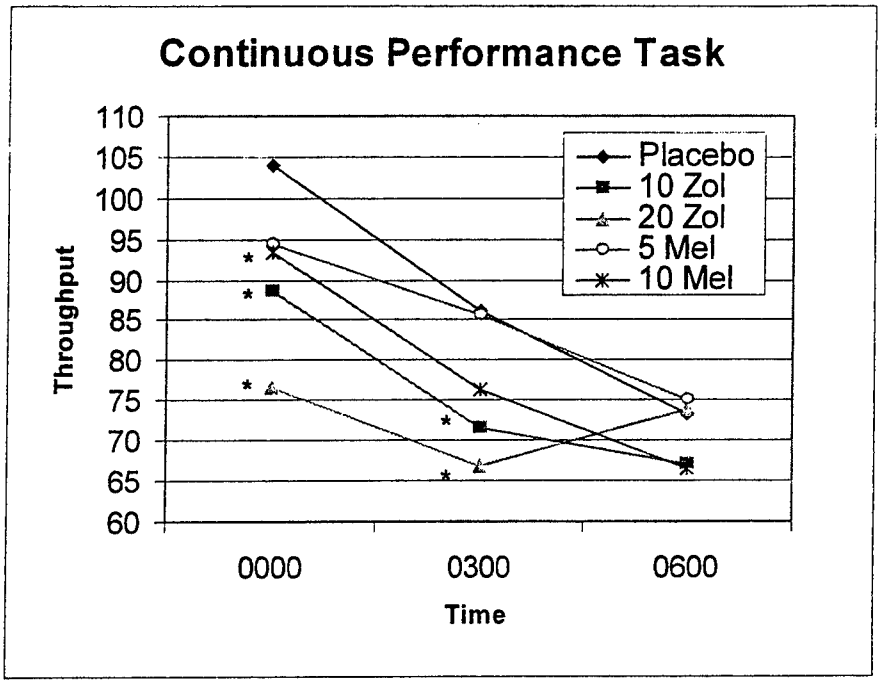

Figure 2. Throughput on the Continuous Performance Test was the only measure to show a Drug by Time interaction. The asterick shows the drug treatment condtions that differed from placebo (alpha = 0.05) at 0000 and 0300.

For mean RT in the Continuous Performance Task, since Drug was significant and Time was close (p=0.092), each drug treatment was also compared to placebo at each time. Interestingly, each drug treatment was significantly different than placebo at 0000 with the zolpidem conditions having the highest RT's. Collapsing across Time, reaction times were significantly longer for the two zolpidem treatments (674 and 676 msec) compared to the placebo (613, p = 0.035 and p = 0.050); RTs for the two melatonin doses (624 and 627 msec) were not different from placebo. Similar results were found for the standard deviation of RT.

As shown in Tables 6-7, dependent measures for most of the tests were sensitive to the effects of the circadian rhythm (Time) and showed poorer performance as the night wore on. There were no effects of morning or afternoon sleep. However, the Time by Sleep Group Interaction was significant for throughput in the Mathematical Processing Test. Figure 3 shows throughput for

the morning sleep group was about 38 at 0000 and decreased over the night to about 29 by 0600, whereas the afternoon sleep group was about 27 and ended the night at about 31 correct responses per minute. Only the AM/PM t-test comparison at 0000 came close to statistical significance, $F(1,12) = 4.48$, $p = 0.056$. However, the between group test has very little power with six in one group and eight in the other.

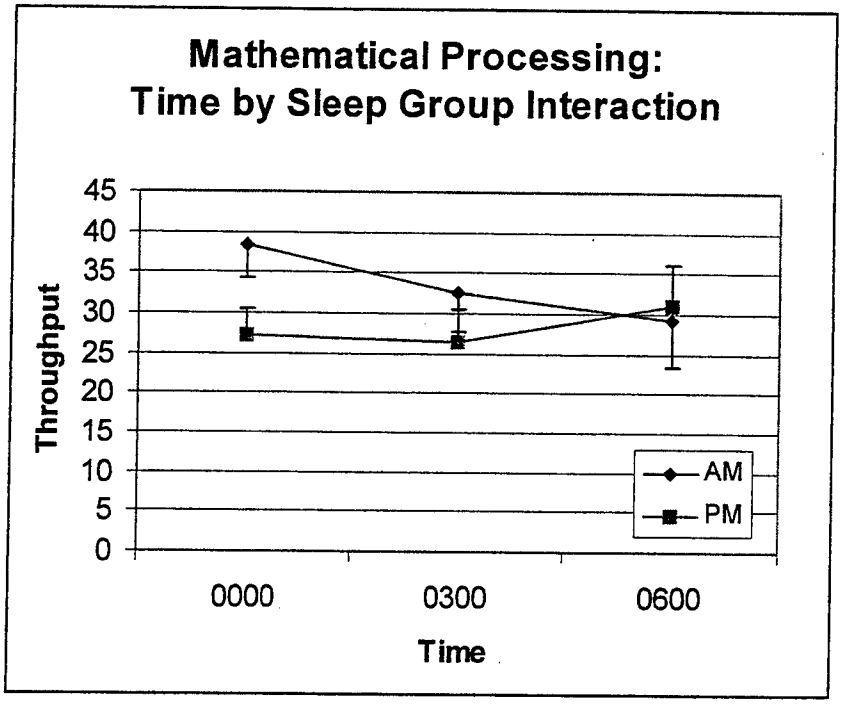

Figure 3. This graph shows the Time by Sleep Group interaction for the throughput measure in the Mathematical processing task. Individual t-tests found no significant differences at any of the times. The standard error of the mean is indicated with bars.

The SynWork Test was used to assess performance in a complex task. From Table 7 it is evident for the composite score that there were significant main effects for Drug and Time, but nothing for Sleep Group or any of the interactions. Figure 4 shows the Drug by Time interaction. Since this task was sampled at later times than the cognitive tests, different circadian effects were observed. Performance degraded until 0500 and then rebounded slightly as the day began. Also, it can be seen from Figure 4 that performance in the two melatonin conditions were insignificantly better than under placebo. Collapsing across Time and testing all drug conditions against each other we found significant effects between the 5 mg and 10 mg melatonin treatments and 20 mg zolpidem ($p = 0.035$ and 0.028, respectively). The composite score means were 5477 (Placebo), 5932 (5 Mel), 5922 (10 Mel), 5409 (10 Zol), and 4575 (20 Zol).

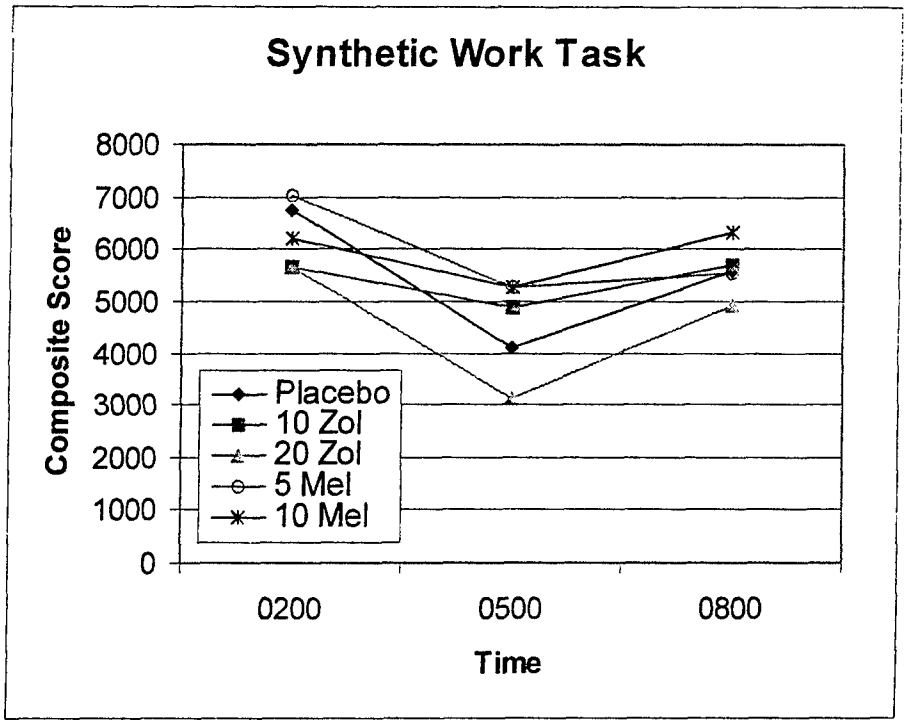

Figure 4. This graph of the composite score for the SynWork task shows inconsistent relations. However, the 20 mg zolpidem treatment is always most degraded. See text for significant relationships.

The Psychomotor Vigilance Test gave similar results with the cognitive tests with significant Time effects for Lapses ($F(2, 22) = 24.65$, $p = 0.001$), Reaction Time (RT) ($F(2, 22) = 7.40$, $p = 0.004$), Reciprocal RT ($F(2, 22) = 56.43$, $p = 0.001$), Standard Deviation of Reciprocal RT ($F(2, 22) = 22.95$, $p = 0.001$) and Standard Deviation of RT ($F(2, 22) = 9.99$, $p = 0.001$). This 10-minute reaction time task was only sensitive to circadian effects; there were no Drug, Sleep Group, or interaction effects. Plots were similar to Figure 1. Collapsing across drug treatments, lapses increased from 4.5 at 0000 to 21 at 0600.

Subjective Reports

Two subjective report scales were used: the Stanford Sleepiness Scale (SSS) and the WRAIR Mood 2. The Mixed ANOVA for each dependent measure for each test included variables for Drug Treatment (5), Time (3) and Sleep Group (2). For the SSS the only variable analyzed was the sleepiness score. For the Mood 2, activity, anger, anxiety, depression, fatigue and happiness were analyzed. Results of the seven ANOVA tests are shown in Table 8. Again what is very clear is that none of the daytime sleep aids significantly improved any of the subjective reports compared to placebo. Figures 5 and 6 show the significant increase in sleepiness and fatigue as the night progresses, Time (circadian) effect. The figures also show that participants reported feeling somewhat sleepier and more fatigued under the two-zolpidem conditions compared to the other drug treatments. While the Drug by Time interaction was not significant, drug treatments at 0000 were for SSS ($F(2,30)$[1] $= 4.05$, $p = 0.023$) and for the Mood 2 fatigue scale ($F(4,52) =$

[1] Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.

4.11, p = 0.006). For SSS, the significant drug treatment effect extended to 0300, but not to 0600.

Table 8. Analysis of the Stanford Sleepiness Scale and the Mood 2 Subjective Reports.

Dependent Measure – Stanford Sleepiness Scale	**Drug F(4,48) = p =**	**Time F(2,24) = p =**	**Sleep Group F(1,12) = p =**	**Significant Interactions**
Score	3.87 0.032*	29.78 0.000*	0.41 0.532	None
Mood 2				
Activity – decreased over time	1.45 0.253	6.85 0.011*	0.629 0.443	None
Anger	1.06 0.371	3.66 0.061	3.85 0.074	None
Anxiety	0.60 0.581	3.87 0.057	0.732 0.409	None
Depression – increased over time and AM sleep group more depressed than PM group	1.38 0.269	8.07 0.004*	5.17 0.042*	Time x Sleep Group F(2,24) = 4.81 p = 0.025*
Fatigue – increased over time	2.95 0.047*	50.67 0.000*	1.53 0.239	None
Happiness – decreased over time	1.68 0.197	11.43 0.001*	1.33 0.271	None
Note: * $p < 0.05$				

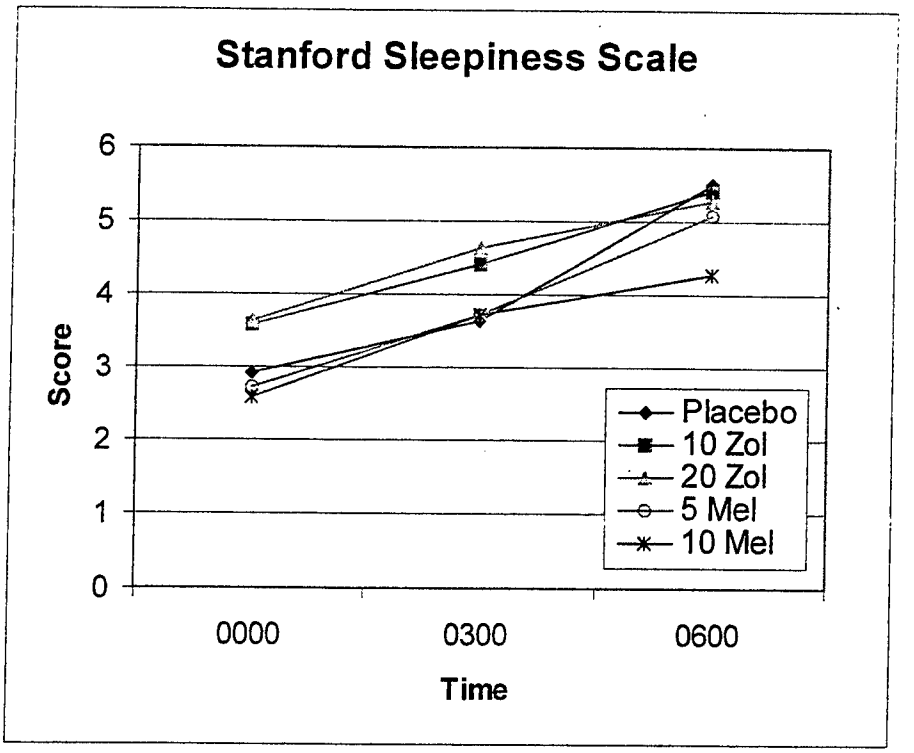

Figure 5. This graph shows the mean scores of the Stanford Sleepiness Scale during the night after the daytime sleep under each of the drug treatments. Larger values reflect greater sleepiness.

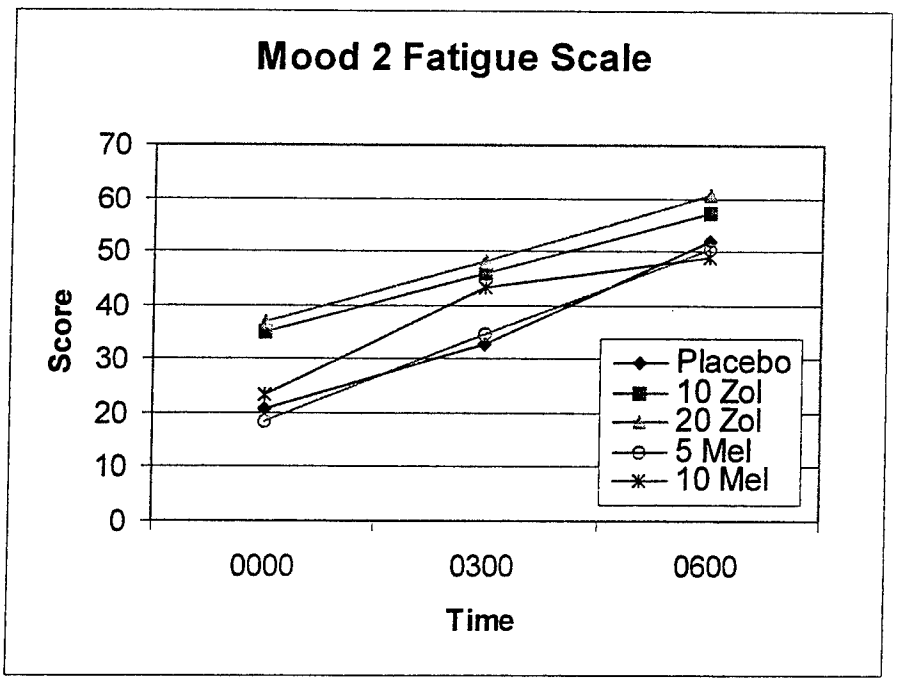

Figure 6. The Mood Survey fatigue scale shows effects similar to the Stanford Sleepiness Scale. Higher values reflect greater fatigue. The Drug by Time interaction was not significant, but the same significant increase in fatigue is shown as the night progresses.

As might be expected both Activity and Happiness decreased over time as the participants became more fatigued. There were no effects of morning or afternoon sleep except that the morning sleep group appeared to be more depressed than the afternoon sleep group, Figure 7, possibly because they had been awake longer. Also shown in Figure 7, depression scores increased as both groups became more fatigued throughout the night. As shown in the full scale graph, none of the mean depression scores rose to clinically significant depression levels.

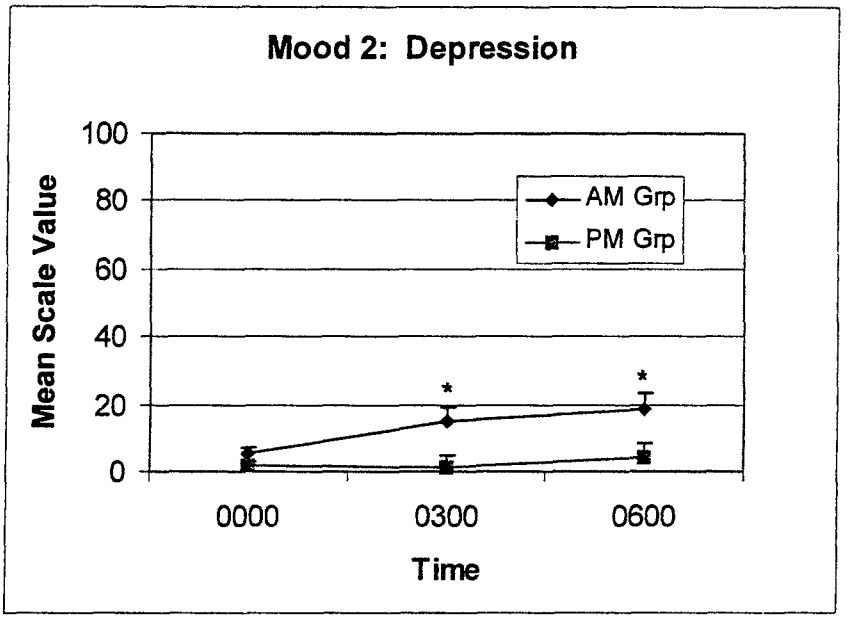

Figure 7. Depression scores increased throughout the night, but were not clinically significant as shown on the full scale from 0 to 100 for Time by Sleep Group interaction. The astericks (*) indicate significant differences between the groups at p = 0.05. The standard error of the mean is indicated with bars.

Since no positive effects of the sleep aids were found under the conditions of this experiment, one immediately wants to know whether there were differences in sleep between the treatment conditions and between morning and afternoon sleep. That is could the lack of performance facilitation be due to the fact that all treatments showed equal sleep?

Sleep as Measured by Polysomnography

Sleep was scored using standard staging methods by a licensed polysomnographer. Table 9 shows the mean time in minutes for the various sleep stages by drug treatments. Percentage of sleep for each stage was also analyzed. On Average, participants received 29-32 extra minutes of sleep under zolpidem compared to placebo and under the high dose of melatonin they slept 36 minutes longer. However, none of the total sleep times (TST) for any of the drug treatments were statistically different from each other ($F(4, 40) = 2.35$, $p = .083$). All participants experienced adequate sleep averaging 6.9 to 7.5 hours across the drug treatments. Individual participants experiencing more awakenings or difficulty sleeping tended to be in the placebo or 5 mg melatonin treatment which likely contributed to TST approaching statistical significance.

No differences were found for sleep efficiency, Stage 3, Stage 4, or REM sleep. The data for sleep latency were corrupted and could not be analyzed. There were significant differences for the drug treatments in the percentage of Stage 1 sleep ($F(4, 40) = 2.95$, $p = 0.032$) with the placebo and 5 mg melatonin condition greatest. Morning and Afternoon sleepers were only different in their percentage and total minutes of Stage 2 sleep ($F(1, 10) = 6.25$, $p = 0.031$ and $F(1, 10) = 8.15$, $p = 0.017$, respectively). The morning sleepers were about 232 while the afternoon sleepers were 268 minutes. No other statistical differences were found.

Table 9. Averaged Number of Minutes in each Sleep Stage by Drug Treatment

	Drug Treatment				
Sleep Stage	Placebo	Zolpidem 20 mg	Zolpidem 10 mg	Melatonin 10 mg	Melatonin 5 mg
REM	79	82	96	89	80
Stage 1*	34	27	25	18	33
Stage 2	232	272	252	264	244
Stage 3	26	20	29	24	20
Stage 4	43	45	41	56	46
Total Minutes	414	446	443	450	423
Note: * $p < 0.05$					

Salivary Melatonin

It was thought that salivary melatonin may have been affected by the manipulations and interventions of this experiment. Although ingested melatonin is short lived, it was thought that it might affect the levels of endogenous melatonin the night after its use. Further that the zolpidem might have an effect on endogenous melatonin in the night following its ingestion. Unfortunately some of the data samples were corrupted and therefore prevented us from analyzing with a standard ANOVA (nearly every subject had one or more missing data points). It was decided to run one-way ANOVAs with five levels of the drug treatment at each time throughout both nights. If there was an effect of a drug treatment it would be present on the second night, not on the first night prior to the treatment. The analyses uncovered no significant drug effects at any time across both nights. A graph of the melatonin in pg/ml across both nights by drug treatment is shown in Figure 8. The spike at 0200 on the second night is due to two female subjects in the AM sleep group having over 200 pg/ml of melatonin. One was in her placebo session and the other the night after her 5 mg melatonin session. The large melatonin hump for the 10 mg melatonin treatment was primarily due to one female subject in the PM sleep group who had over 100 pg/ml. Based on a review of the individual subject data and the ANOVA results the best assessment would be to conclude that salivary melatonin was not affected by any of the conditions of this experiment.

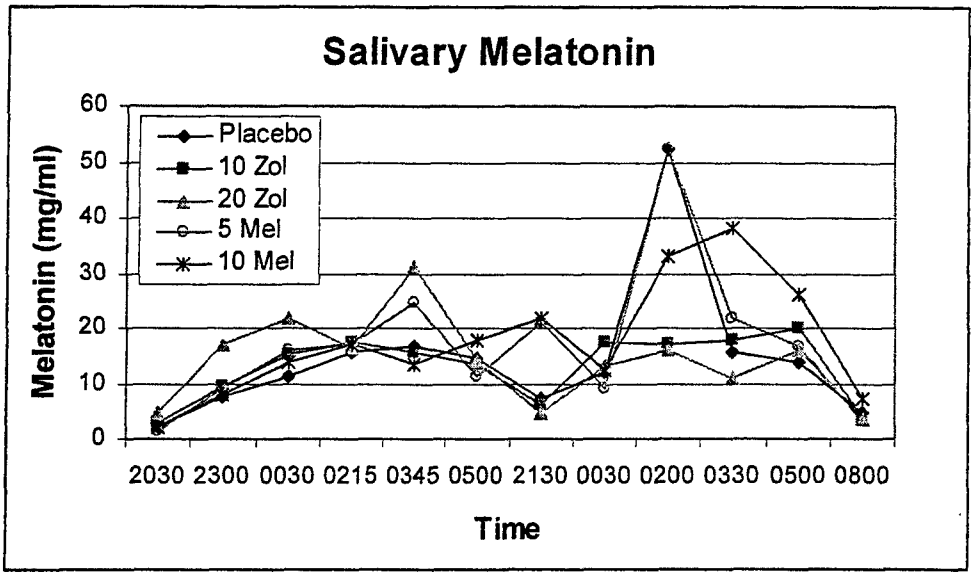

Figure 8. This is a plot of salivary melatonin during the work nights before and after sleep under the drug treatments.

Sleep Inertia Effects

Sleep inertia implies that some aspect of sleep somehow continues after awakening with the result that performance is degraded. In this study, performance after awakening can be analyzed. However, sampling performance at two different times in the circadian rhythm confounds a comparison between the two sleep groups. If there are differences between the two groups, it could be because sleep inertia is effected by different sleep times or because our performance measurements were taken at different times in the circadian rhythm.

Cognitive Performance Tests

Mixed ANOVAs for each dependent measure in each test included variables for Drug Treatment (5) and Sleep Group (2). For each test, accuracy, reaction time (RT), standard deviation of RT (SDRT), throughput and percent of missed trials were analyzed as before. The dependent measures of the Psychomotor Vigilance Test (PVT) were also analyzed and included with the results for the cognitive tests: lapses, reaction time, reciprocal RT, standard deviation of reciprocal RT, and standard deviation of RT. The performance test data taken within 3 to 30 minutes of awakening show that the drug treatments given eight and a half hours before sleep deepened the effects of sleep inertia compared to our placebo control condition. Table 10 shows the results of the 28 ANOVA tests on the performance measures. Each of the 18 statistically significant Drug effects was further analyzed by comparing each drug treatment with the placebo treatment. The 20 mg zolpidem treatment was significantly degraded in 13 of the tests, the 10 mg zolpidem treatment was degraded in 7 and the 10 mg melatonin treatment was degraded in 4 of the tests. The 5 mg melatonin treatment was never different than placebo. Figure 9 displays the drug treatment means for the Continuous Performance Task and is typical of the cognitive performance measures showing degradation for the two zolpidem treatments and the 10 mg melatonin treatment. The 10 mg melatonin treatment is often between the performance levels of the 10 mg zolpidem treatment and placebo; and typically not significantly different than placebo.

Table 10. The Effects of Drug Treatments and Sleep Time on Performance Test Measures Immediately Upon Awakening.

Dependent Measure –	Drug F(4,48) = , p =	Sleep Group F(4,48) = , p =	Drug by Sleep Group F(4,48) = , p =
Simple Reaction Time			
Reaction Time	2.48, 0.039*	0.15, 0.706	0.52, 0.724
SD of Reaction Time	3.02, 0.027*	2.03, 0.180	0.27, 0.894
Percent of Missed Trials	1.19, 0.321[1]	1.77, 0.681	3.07, 0.064
Logical Reasoning			
Accuracy	3.83, 0.037[1]*	0.76, 0.400	1.09, 0.372
Reaction Time	1.51, 0.238[1]	0.48, 0.503	0.59, 0.671
SD of Reaction Time	4.18, 0.006*	0.00, 1.000	0.32, 0.865
Throughput	3.81, 0.026[1]*	0.12, 0.737	1.73, 0.158
Percent of Missed Trials	1.55, 0.227[1]	1.61, 0.228	0.88, 0.484
Continuous Performance			
Accuracy	4.41, 0.020[1]*	0.63, 0.444	1.68, 0.170
Reaction Time	3.12, 0.018*	1.01, 0.336	1.69, 0.168
SD of Reaction Time	1.66, 0.174	2.99, 0.110	0.89, 0.477
Throughput	5.67, 0.003[1]*	0.79, 0.392	0.92, 0.460
Percent of Missed Trials	2.54, 0.117[1]	0.00, 0.964	0.65, 0.628
Mathematical Processing			
Accuracy	3.66, 0.031[1]*	1.68, 0.220	0.53, 0.713
Reaction Time	4.83, 0.002*	2.87, 0.116	0.71, 0.592
SD of Reaction Time	4.23, 0.005*	1.84, 0.200	0.525, 0.647
Throughput	5.39, 0.001*	3.60, 0.082	0.42, 0.792
Percent of Missed Trials	2.98, 0.067	0.65, 0.437	0.59, 0.670
Delayed Match-to-Sample			
Accuracy	3.26, 0.019*	0.52, 0.484	1.42, 0.243
Reaction Time	2.93, 0.030*	0.27, 0.612	0.80, 0.530
SD of Reaction Time	0.98, 0.409[1]	0.24, 0.636	1.50, 0.216
Throughput	3.15, 0.022*	0.00, 0.957	0.56, 0.692
Percent of Missed Trials	0.54, 0.710	0.02, 0.897	1.22, 0.314
Psychomoter Vigilance Task			
Lapses	4.53, 0.013[1]*	0.64, 0.439	0.92, 0.462
MRT	1.10, 0.362	0.14, 0.717	1.45, 0.232
MRRT	6.07, 0.001*	1.31, 0.275	2.10, 0.095
SDRRT	2.85, 0.034*	0.28, 0.605	1.39, 0.252
SDRT	1.08, 0.371	0.00, 0.966	1.43, 0.239

Notes:
[1] Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.
* $p < 0.05$

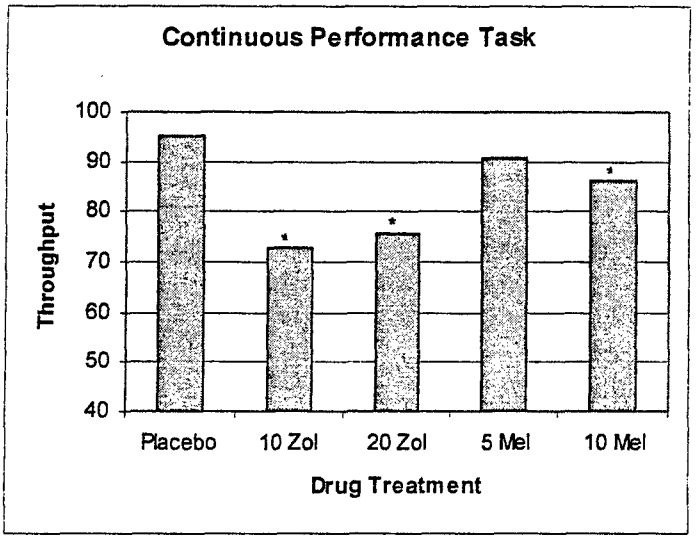

Figure 9. This graph shows the degrading effects of zolpidem and the 10 mg dose of melitonin on Continuous Performance throughput upon awakening compared to placebo. An asterisk (*) indicates a significant difference with placebo at $p < 0.05$.

Subjective Reports

Mixed ANOVAs for each subjective report dependent measure included variables for Drug Treatment (5) and Sleep Group (2). The subjective report data taken within 3 to 15 minutes of awakening show that the drug treatments given eight and a half hours before sleep deepened the effects of sleep inertia compared to the placebo treatment. Table 11 shows the results of the 7 ANOVA tests on the subjective report scores. Each of the 3 significant Drug effects was further analyzed by comparing each drug treatment with placebo. Participants in the 20 mg zolpidem treatment were significantly more angry and fatigued than under placebo and in the 5 mg melatonin treatment more active than under the placebo. Figure 10 shows a plot of the fatigue scale means and is typical of the other measures showing significantly more fatigue under 20 mg of zolpidem with the 10 mg zolpidem and melatonin treatments approaching levels similar to the placbo. The Stanford Sleepiness Scale trended in the same direction for the zolpidem conditions as did the anxiety measure and participants trended toward less happiness under zolpidem as well.

Table 11. The Effects of Drug Treatments and Sleep Time on Subjective Report Measures Immediately Upon Awakening.

Dependent Measure –	Drug F(4,48) = , p =	Sleep Group F(4,48) = , p =	Drug by Sleep Group F(4,48) = , p =
Stanford Sleepiness Scale			
Score	2.02, 0.106	0.02, 0.893	1.49, 0.221
Mood 2			
Activity	2.57, 0.050*	0.02, 0.879	0.10, 0.982
Anger	4.18, 0.043[1]*	1.09, 0.317	3.51, 0.064[1]
Anxiety	1.75, 0.156	0.00, 0.983	1.51, 0.213
Depression	0.76, 0.560	4.10, 0.066	1.16, 0.339
Fatigue	3.01, 0.027*	1.15, 0.305	0.46, 0.768
Happy	1.22, 0.314	0.01, 0.906	0.16, 0.958

Notes:
[1] The Huynh-Feldt adjustment was applied to the ANOVA degrees of freedom.
* $p < 0.05$

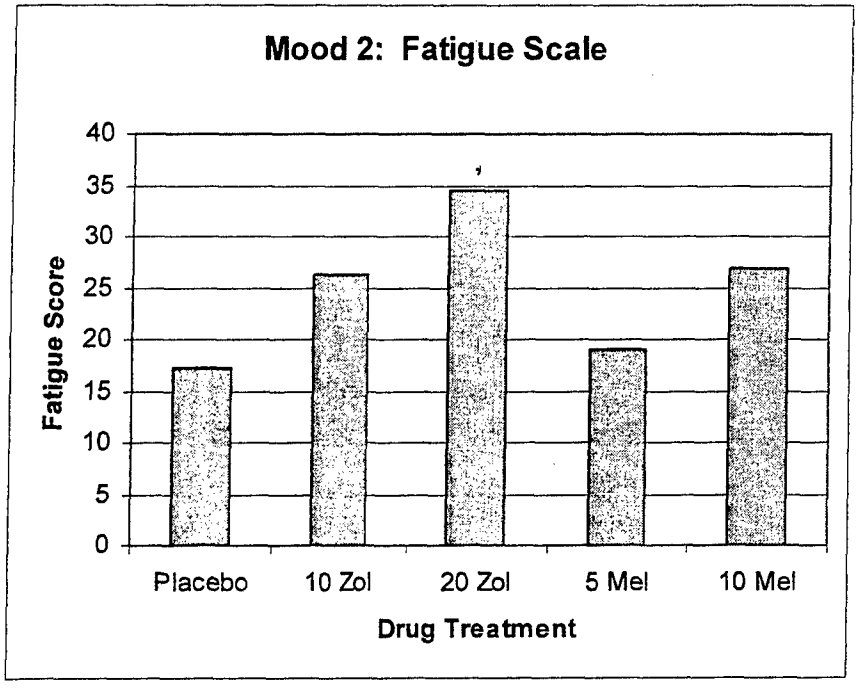

Figure 10. This graph shows the drug treatment means for the fatigue scale immediately upon awakening. The asterisk (*) indicates a significant difference with placebo, $p < 0.05$.

DISCUSSION

Night Work Effects

Contrary to contemporary wisdom, none of the measures in this study showed a performance improvement with any of the sleep aids tested. Neither zolpidem nor melatonin was successful in improving daytime sleep compared to placebo. The measures that did show a drug effect were negative for zolpidem, specifically the Continuous Performance Test and the Synthetic Work Task. Subjective reports of sleepiness and fatigue supported the performance effects for zolpidem. If people have difficulty sleeping during the daytime, this study did not find that to be the case under the conditions of the experiment. Although participants slept more under zolpidem and 10 mg of melatonin, the difference was not statistically significant. What could be the cause for this non-intuitive finding?

> Explanation 1: Because participants were sleep deprived the previous night all participants slept for nearly the full 8 hours, there were no differences in sleep and therefore no benefit to performance or mood from the sleep aids.
>
> Explanation 2: Sleep aids given during the day are not useful for banking sleep beyond a good opportunity for sleep whether sleep deprived or not. If we found that there were differences in sleep among the conditions, then we would have to conclude that those differences were not sufficient to affect performance the following night.

The placebo treatment slept on average 6.9 hours, the 20 mg zolpidem treatment slept 7.4 hours. These data do not seem to definitively support one explanation over the other, but they do lean toward Explanation 2. Sleep was better for the zolpidem treatment, but not significantly, therefore, we could conclude that there were no differences in sleep and there should be no differences in performance. The cause for the good, daytime sleep in the placebo group may be attributable to the near perfect sleeping environment of the temporally isolated FCL or to the sleep deprivation of the night before. Both could cause the participants to sleep more than usual. However, Dr. Lynn Caldwell (Caldwell, Hall, Prazinko, Norman, Rowe, Erickson, Estrada & Caldwell, 2002) found that her participants in her temazepam study slept 6.5 hours under the placebo condition and 7.8 hours under the drug. She too found no difference in performance the night following the first day sleep. However, she found that after the second day of sleep and night work, that the additional minutes of sleep did begin to affect performance and mood in a positive way.

Another non-intuitive finding of this study was that there was no advantage for morning or afternoon sleepers regarding nighttime alertness, mood or performance. The Foret and Lantin (1972) findings of 3-4 hours of sleep during the day do not appear to hold for sleep deprived people sleeping under ideal conditions. For two consecutive work nights, ideal daytime sleeping conditions appear to provide nearly as much sleep as a sleep aid and without any risk to nighttime performance. This is a very important finding for aircrew who must follow a reverse schedule of daytime sleep and night work. If they can obtain quiet, dark, cool quarters for sleep, get proper nutrition, and avoid alcohol, they will likely acquire enough restorative sleep to function throughout a single night of work.

Sleep Inertia Effects

Sleep inertia implies that some aspect of sleep somehow continues after awakening with the result that performance is degraded. In this study, performance after awakening was found to not be different for morning or afternoon sleepers, but performance was found to be degraded by sleep aids compared to the placebo treatment. Considering the significant performance degradation found in the Continuous Processing and SynWork tasks and the subjective reports of more fatigue and sleepiness at 0000, the sleep inertia findings are problematic for the 20 mg dose of zolpidem and possibly for the 10 mg dose as well. Trends in the dependent measures of the other performance tests at 0000 (Mathematical Processing, Matching to Sample, Logical Reasoning and PVT) bolsters this finding. However, looking at the Time by Drug by Sleep Group graphs (not shown) it was apparent that the PM sleep group suffered more degradation than the AM group. This effect was evident in the Time by Sleep group interaction of the Mathematical Processing task shown in Figure 3. These observations along with the knowledge that the power for the between group tests was low (less than 50%), allow one speculate on a possible interpretation for the negative findings. If the primary reason for the negative effects at 0000 was due to the PM sleep group, a logical explanation would be that zolpidem continued to circulate in the blood system and cognitively combined with sleep inertia in the PM group to degrade performance upon awakening. The Time by Drug by Sleep Group interaction was not significant because of the low power of the test. The study was not designed for examining such an effect and would have needed additional participants in the two groups.

Although it would be tempting to analyze the AM group's performance after their awakening sample at 1900, with an n = 6 there would not be enough power to test the hypothesis that residual zolpidem was combining with sleep inertia to degrade performance. In this study, the performance degradation from zolpidem primarily in the PM sleep group appears to last two or more hours after awakening from eight hours of sleep. Based on the findings of this study, the AFSG recommendation for taking zolpidem of no less than 12 hours prior to show time is adequate and should not be shortened.

CONCLUSIONS

In this study, neither zolpidem nor melatonin was successful in improving daytime sleep compared to placebo. Participants slept longer under the medicated treatments, but it was not statistically significant. Given the sleep outcome, it was not surprising that there were no differences among the sleep aid conditions for alertness, mood or performance. After 24 or more hours of sleep deprivation, excellent sleeping conditions appear to provide nearly as much sleep as a sleep aid (zolpidem or melatonin) for maintaining performance. Sleep inertia may be deepened by the use of zolpidem and may prolong degraded performance, sleepiness and fatigue beyond that occurring naturally. More research is needed to confirm these sleep inertia findings and to systematically vary the quality of sleep to better approximate the conditions of sleep found in operational units

REFERENCES

AFMOA/CC Memorandum (25 October 2001). Revised duty limitation times for the ground testing and operational use of tamazepam, zolpidem, and zalaplon in aviators and special duty personnel.

Baddeley, A.D. (1968). A 3 minute reasoning test based on grammatical transformation, *Psychonomic Science, 10(10)*, 341-342.

Caldwell, J.L., Hall, K.K., Prazinko, B.F., Norman, D.N., Rowe, T., Erickson, B.S. Estrada, A., & Caldwell, J.A. (2002). *The efficacy of temazepam for improving Dayton sleep and nighttime performance in Army aviators*. Army Aeromedical Research laboratory Technical Report, No. 2002-05.

Cohen, J (1988). *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum Associates, Hillsdale NJ

Cole, R.J., Kripke, D.F., Gruen, W., Mulaney, D.J. and Gillin, J.C. Automatic sleep/wake identification from wrist activity. Sleep. 1992; 15(5), 461-469.

Dawson, D., Gibbon, S., & Singh, P. The hypothermic effect of melatonin on core body temperature: was more better. Journal of Pineal Research 1996; 20(4): 192-197.

Dinges, DF, Pack, F, Williams, K, Gillen, KA, Powel,l JW, Ott, GE, Aptowicz, C, & Pack, AI (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep, 20, 267-277.

Drug Digest website (2004). Melatonin, www.drugdigest.org/DD/DVH/HerbsWho/0,3923,4060%7Cmelatonin,00.html. (Revised 12 May 2004).

Foret, J., Lantin, G. The sleep of train drivers: an example of the effects of irregular work schedules on sleep. Pages 273-282 in WP Colquhoun (ed.), Aspects of Human Efficiency, The English Universities Press, London, 1972.

Griebel, G., Perrault, G., Letang, V., Granger, P., Avenet, P., Schoemaker, H., & Sanger, D.J. New evidence that the pharmacological effects of benzodiazepine receptor ligands can be associated with activities at different BZ(omega) receptor subtypes. Psychopharmacology (Berlin). 1999; 146(2): 205-213.

Hoddes, E, Zarcone, VP, Smythe, H, Phillips, R, & Dement, WC (1973). Quantification of sleepiness: A new approach. Psychophysiology, 10, 431-436.

Hughes, R.J., Badia, P., French, J., Santiago, L., & Plenzler, S. Melatonin induced changes in body temperature and daytime sleep. Sleep Research. 1994; 23: 496.

Morgan, P.J., Barrett, P., Howell, H.E., & Helliwell, R. Melatonin receptors: localization, molecular pharmacology and physiological significance. Neurochemistry International. 1994; 24(2): 101-146.

Mitler, MM, Carskadon, MA, & Hirshkowitz, M (2000). Evaluating sleepiness. Chapter 104 In MH Kryger, T Roth, & WC Dement (Eds.), Principles and Practices of Sleep Medicine (3rd ed.), WB Saunders, Philadelphia.

Pollard, J. K. (1996) *Locomotive Engineer's Activity Diary. Final Report*, DOT/FRA/RRP-96/02, DOT-VNTSC-FRA-96-12, U.S. Department of Transportation, Federal Railroad Administration, Office or Policy and Program Development and Office of Research and Development, Washington, D.C. 20590.

Rea, M.A. and Pickard, G.E. A 5-HT1B receptor agonist inhibits light-induced suppression of pineal melatonin production. Brain Research. 2000; 858: 424-428.

Reid, K., Roach, G, and Dawson, D. (1997). The proportion of time spent sleeping and working across the day in train drivers working irregular hours. *Sleep Research, 26.*

Ryman, D.H., Biersner, R.J., & LaRocco, J.M. (1974). Reliabilities and validities of the mood questionnaire. *Psychological Reports, 35,* 479-484.

Salva, P. & Costa, J. (1995). Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. *Clinical Pharmacokinetics; 29*(3), 142-153.

Sanofi-Synthelabo Inc. website (2002). Ambien® (zolpidem tartrate), www.ambien.com.

Shochat, T., Luboshitzky, R., & Lavie, P. (1997). Nocturnal melatonin onset was phase locked to primary sleep gate. *American Journal of Physiology, 273,* R364-370.

Stanny, R.R. (1990). Modeling for Human Performance Assessment. Annual Report. Office of Military Performance Assessment Technology, Washington DC.

Thorne, D. (1991). Throughput: A simple, rational performance index with desirable characteristics. *OMPAT Electronic Bulletin Board-Performance Information Management System.* Walter Reed Army Institute of Research, Washington, D.C.

Thorne, D., Genser, S., Sing, H., & Hegge, F. (1985). The Walter Reed Performance Assessment Battery. *Neurobehavioral Toxicology and Teratology, 7,* 415-418.

Tosini, G. and Dirden J.C. (2000). Dopamine inhibits melatonin release in the mammalian retina: in vitro evidence. *Neuroscience Letters, 286,* 119-122.

APPENDICES

Appendix A: Melatonin analysis process
Appendix B: Activity Log
Appendix C: Six-Week Sequence for a Flight of Participants

Appendix A: Melatonin Analysis Process

Method: Direct Saliva Melatonin RIA

The Direct Saliva Melatonin RIA kit measures melatonin by a double-antibody radioimmunoassay based on the Kennaway G280 anti-melatonin antibody. Undiluted human saliva samples and reconstituted standards and controls are incubated with the anti-melatonin antibody and ^{125}I melatonin. ^{125}I melatonin competes with melatonin present in samples, standards and controls. After 20 hours of incubation, a solid-phase second antibody is added to the mixture in order to precipitate the antibody bound fraction. After aspiration of the unbound fraction, the antibody bound fraction of ^{125}I melatonin is counted. Results are reported as melatonin (pg/ml).

The work was performed by
Endocrine Core Lab
Yerkes Research Center
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404-727-9354
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http://www.emory.edu/WHSC/YERKES/DIV/RSRCHRES/assay/

Kits for Saliva Melatonin RIA came from:
ALPCO Diagnostics
Windham, NH 03087
1-800-592-5726

Appendix B: Activity Log

Activity Log

Date:_____ **Participant #**_____

Time of Day	0000	0100	0200	0300	0400	0500	0600	0700	0800	0900	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000	2100	2200	2300
Sleep																								
Rating																								

Date:

Time of Day	0000	0100	0200	0300	0400	0500	0600	0700	0800	0900	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000	2100	2200	2300
Sleep																								
Rating																								

Date:

Time of Day	0000	0100	0200	0300	0400	0500	0600	0700	0800	0900	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000	2100	2200	2300
Sleep																								
Rating																								

SLEEP SYMBOLS
Write in the appropriate code in the sleep row.
S = Sleep
T = Trying to sleep

UPON AWAKENING from a sleep or nap please rate the quality of your rest by putting one of the numbers below in the sleep row.
1= Well Rested **3= Slightly Rested**
2= Moderately Rested **4= Not at all Rested**

SLEEPINESS RATING
Please indicate your fatigue every four hours that you are awake (0000, 0400, 0800….).
1 - Feeling active and vital; alert; wide awake.
2 - Functioning at a high level, but not at peak; able to concentrate.
3 - Relaxed; awake; not at full alertness; responsive.
4 - A little foggy; not at peak; let down.
5 - Fogginess; beginning to lose interest in remaining awake; slowed down.
6 - Sleepiness; prefer to be lying down; fighting sleep; woozy.
7 - Almost in reverie; sleep onset soon; lost struggle to remain awake.

Appendix C: Six-Week Sequence for a Flight of Participants

Week 1 Only - Training and Orientation

M-W Train participants on test battery to achieve asymptotic performance levels:
- 6 Testing cycles x 3 evenings, 1800-2100 (9 hours for pay)
- Actigraphy and Sleep Log (continues through 6 weeks)

Week	Day	Time	Procedure
Week 1 Only	**Training and Sleep Baseline**		
	Thur.	1800-1830	Arrive, Attach sensors
		1830-2000	2 Testing cycles for training
		2000-2030	*Break – eat and drink*
		2030-2100	1 Testing cycle for training
		2100-0600	Personal time, 8 hrs bed time, 1 Testing cycle for training
	Fri.	0600-0700	2 Testing cycles for training
		0700-0730	Prepare for Work (Shower, eat)
		0730	Released *(Time off from experiment to participate in normal daytime employment)*
	Experimental Treatment Weeks		
Week 1	Fri.	1900-2000	Arrive back at lab, Attach instruments *(participants to eat before they arrive).*
	Testing as indicated in Table 3 – Dose 1 given at time for group (AM or PM)		
	Mon.	0700-0730	Prepare for work, release participants
Week 2	Same as Week 1 (with Training and Sleep baseline omitted) – Dose 2		
Week 3	Same as Week 1 (with Training and Sleep baseline omitted) – Dose 3		
Week 4	Same as Week 1 (with Training and Sleep baseline omitted) – Dose 4		
Week 5	Same as Week 1 (with Training and Sleep baseline omitted) – Dose 5		
Week 6	Actigraphy and sleep log, no testing		